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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/620,820	07/21/2000	Alan D. Attie	960296.97290	4397

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03/25/2003

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EXAMINER

QIAN, CELINE X

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 03/25/2003

60

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/620,820

Applicant(s)

ATTIE ET AL.

Examiner

Celine X Qian

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) 13-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 July 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: Notice to Comply

DETAILED ACTION

Claims 1-16 are pending in the application. Claims 13-16 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1-12 are under examination.

This Office Action is in response to the Amendment filed on 1/8/03.

Response to Amendment

The objection to the specification has been withdrawn in light of Applicants explanation.

The rejection of claims 1-12 under 35 U.S.C.112 2nd paragraph has been withdrawn in light of Applicants' amendment of the claims.

The requirement for sequence compliance is not met for reasons on the CRF problem report and discussed below.

Claims 1-12 are rejected under 35 U.S.C.112 1st paragraph (written description and scope of enablement) for reasons set forth of the record and further discussed below.

Claims 1-12 are rejected under 35 U.S.C.103(a) for reasons set forth of the record and further discussed below.

Claims 1-12 are rejected under 35 U.S.C.112 2nd paragraph for reasons discussed below.

Response to Arguments

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for

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the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

The CRF is damaged.

Claim Rejections - 35 USC § 112

In response to the claim rejection of the previous office action, Applicants argue that the amendment has overcome written description, enablement rejection and 103 rejection.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . . [emphasis added]." The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

The specification discloses that a soluble truncated low density lipoprotein receptor (LDLR), LDLR354, tagged with ER retaining signal KDEL, is able to decrease apoB secretion

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in vitro and *in vivo* thus reduce LDL synthesis. The claims encompass a genus of LDLRs that do not include the domain of the native protein associated with membrane binding. The specification does not teach which part(s) of the LDLR354 is functional in such effects, and whether such fusion protein made with other LDLRs that do not include the domain of the native protein associated with membrane binding would have the same effects. As such, the structural functional relationship between the truncated LDLRs and its function of lowering serum cholesterol and triglyceride is missing. Therefore, the specification fails to describe the invention in such a way to reasonably convey one skilled in the art that the inventors have possession of the invention at the time of filing.

The claims also recite "localization domain which directs localization of the fusion protein to the interior of a cell." Such localization domain encompasses potentially a large genus of signal peptide including localization to nucleus, mitochondria or cytosol. The specification discloses tagging KDEL to the LDLR354 retains the receptor to ER. The specification also discloses several ER retaining signal including KDEL, KEEL, HDEL, DDEL, QDEL, ADEL and SDEL. However, the specification does not disclose other localization domain(s) which directs localization of the fusion protein to the interior (other than ER) of a cell. It appears that the function of the receptor to lower serum cholesterol and triglyceride is based on its retention in ER. It is unclear whether LDLR attached with other signal peptide would have this function. Therefore, the specification fails to describe the invention in such a way to reasonably convey one skilled in the art that the inventors have possession of the invention at the time of filing.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the lowering of serum cholesterol or triglyceride levels in an individual comprising the steps of: preparing a nucleic acid construct comprising a DNA sequence encoding a fusion protein comprise LDLR354 and a signal peptide which retains the fusion protein in ER, operatively linked to a promoter; administering the nucleic acid construct systemically to a mammal, wherein expression and production of said fusion protein results in the lowering of serum cholesterol in said mammal, does not reasonably provide enablement for a method for lowering the serum cholesterol or triglyceride levels in an individual comprising the steps of: making a genetic construct comprising a protein coding sequence encoding for the expression of a fusion protein including any lipoprotein receptor do not have a membrane binding domain, and any localization domain directs the fusion protein to the interior of a cell, operatively linked to a promoter, and delivering the genetic construct into the individual. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The nature of the invention is a method of lowering serum cholesterol or triglyceride in an individual comprising the step of making a genetic construct comprising (1) a protein coding sequence encoding for the expression of a fusion protein including a low density lipoprotein receptor without the native membrane binding domain, and a localization domain which directs localization of the fusion protein to the interior of a cell in the individual, and (2) a promoter effective in the cells of the individual to express the protein encoding sequence; and delivering the genetic construct into the individual. In the example given in the specification, applicants disclose a fusion protein encoding a truncated soluble LDLR, LDLR354, linked to an

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endoplasmic reticulum (ER) localization sequence, KDEL, which is capable of decrease hepatic apoB secretion both *in vitro* and *in vivo*. The specification further discloses that serum LDL is lowered when this construct is injected through tail vein of the mice.

The breath of the claims is broad. The broadest claim is drawn to a method of lowering serum cholesterol by making a construct comprising a nucleic acid encoding a fusion protein comprising (1) a protein coding sequence encoding for the expression of a fusion protein including a low density lipoprotein receptor without the native membrane binding domain, and any localization domain which directs localization of the fusion protein to the interior of a cell in the individual, and (2) a promoter effective in the cells of the individual to express the protein encoding sequence; and delivering the genetic construct into the mammal by any routes.

The teaching of the specification is limited. The specification only teach administering a fusion protein of LDLR354 tagged with KDEL to the tail vein of the mouse result in decreased cholesterol. The specification fails to teach other LDLR without membrane binding domain tagged with any localization domain, for example, tat, which directs localization to nucleus would achieve the same effect. The specification fails to teach any other route of administration such as oral, intramuscularly, or topical administration of said construct would lower serum cholesterol or triglyceride. Without teaching from the specification, one skilled in the art would have to turn to prior art for guidance to practice the claimed method.

As discussed in the previous office action, the state of art at the time of filing teach that increased LDLR level reduces apoB secretion in hepatic cells, because the interaction between LDLR and apoB in the lumen of ER could make apoB more protease accessible thereby facilitates the degradation of apoB. It is well known that apoB is a necessary component of

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VLDL/LDL synthesis. Therefore, decreasing apoB secretion would lower serum cholesterol and triglyceride by decreasing VLDL/LDL synthesis.

The state of art at the time of filing considers the success of gene therapy as unpredictable. Verma et al. (1997, Nature, Vol. 389, pages 239-242), Anderson et al. (1998, Nature, Vol. 392, pages 25-30), and Palu et al. (1999, Journal of Biotechnology, Vol. 68, pages 1-13) discuss the inherent difficulties in gene therapy. The major difficulties include poor delivery systems and poor gene expression after delivery (see Anderson, page 30, 1st col., 5th paragraph). Another factor that affects the efficacy of gene therapy methods is the immune system of the host organism (see Palu, page 9, 1st col., 2nd paragraph, lines 1-5). The host immune system rejects the foreign cell that is introduced to said host thus prevents the expression of the gene within the cell. Therefore, in view of the above technical difficulties, one of skilled in the art would have to rely on the teaching of the specification to practice the method as claimed.

The specification only teaches a method of lowering serum cholesterol level by administering a construct encoding a fusion protein comprising LDLR354 tagged with KDEL and operatively linked to a promoter effective in the cells of the individual to express the fusion protein to the tail vein of a mice. Thus, the specification is only enabled for this scope. It does not provide support for such a method by administering the construct by any route (other than systemic administration). In addition, the specification also fails to support such a method wherein the LDLR is tagged with any other localization domain that directs the fusion protein to any part of the interior of the cell (other than ER). One skilled of art would have to engage in undue experimentation to practice the method in commensurate with the scope of these claims.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "the fusion protein including a low density lipoprotein receptor which does not include the domain of the native protein associated with membrane binding and a localization domain..." renders the claims indefinite because it is unclear what the fusion protein comprises. It is confusing whether this fusion protein includes the localization domain or not. If it does not comprise the localization domain, then what is the receptor fused to?

Claim Rejections - 35 USC § 103

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Twisk et al., in view of Teasdale and Jackson and Attie et al. (5,521,071).

Twisk et al. teach that expression of LDLR decreased apoB secretion in a LDLR-/- knockout mouse model (see page 527, 1st column, last paragraph). Twisk et al. further propose a model of apoB secretion and degradation pathway (see page 530, figure 7, and 1st column, 1st paragraph): "As apoB enters the secretory pathway, presecretory degradation occurs via both LDL receptor-dependent and -independent mechanisms. A temporary arrest of apoB translocation, or an extended association between apoB and the translocon as it enters the ER, could facilitate an interaction between apoB and the LDLR. Rapid and slow presecretory apoB degradation may occur in the ER or in a post-ER compartment. The nascent lipoprotein particle ultimately reaches the cell surface, where the LDLR can mediate its reuptake, resulting in internalization and subsequent turnover of apoB." However, Twisk et al. does not teach a LDLR

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comprising a KDEL ER retaining signal. Twisk et al. does not teach a method of lowering serum cholesterol and triglyceride by administering a construct encoding LDLR354 and KDEL to a mammal.

Teasdale and Jackson teach that KDEL is a ER retaining signal that is capable of retrieving soluble KDEL-tagged molecules back to ER (see page 36, last paragraph).

Attie et al. teach a construct encoding LDLR354, a soluble LDLR which also retains affinity for binding to LDL (Figure 2). The truncation is a carboxyl terminal truncation of the native LDLR gene which does not contain the membrane binding domain of the native gene (bridging paragraph of col.3 and 4).

It would have been obvious to one of ordinary skill in the art to make a construct comprising a soluble LDL tagged with a ER retaining signal such as KDEL and use it in a method to decrease serum cholesterol or triglyceride in a mammal based on the combination teaching of Twisk et al., Teasdale and Jackson and Attie et al. One of ordinary skill in the art would be motivated to do so because Twisk et al. teach that LDLR facilitates presecretory apoB secretion in ER and post-ER compartment. It is well known in the art that apoB is a necessary component of lipoprotein particle, including LDL and VLDL. It would be obvious to one of ordinary skill of art who intend to lower serum cholesterol in a patient to decrease apoB secretion, thus lower LDL synthesis. Attie et al. teach a soluble LDLR which retains LDL binding. Teasdale et al. teach signal peptide that is capable of retrieving soluble KDEL tagged molecules back to ER. The skill of art in molecular cloning is high. Absent evidence from the contrary, one of ordinary skill of art would have reasonable expectation of success to make a construct as claimed, and administer the construct systematically to a mammal to lower its serum

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cholesterol or plasma triglyceride. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
March 21, 2003

Anne-Marie Falk
ANNE-MARIE FALK, PH.D.
PRIMARY EXAMINER

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☒ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☐ 7. Other: _____

Applicant Must Provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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